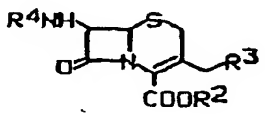
SPECIFICATION

1. TITLE OF INVENTION

PROCESS FOR ELIMINAITON OF FORMYL GROUP

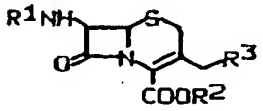
2. CLAIMS

A process for preparing a compound of the formula:

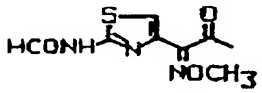


R S - cefpodoxime proxetil
by eliminating formyl group
of N-formyl-cefpodoxime
proxetil

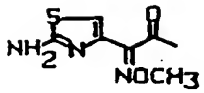
or its salt, which is characterized by treating a compound of the formula:



with methanesulfonic acid or trifluoromethanesulfonic acid
(wherein R1 is a formyl group or a group of the formula:



, R2 is a 1-alkoxycarbonyloxyethyl group or an anion, R3 is an alkoxy group or a thazolio group optionally substituted with alkyl and/or hydroxyalkyl and R4 is a hydrogen atom or a group of the formula:



3. DETAILED EXPLANATION OF INVNETION

Object of Invention:

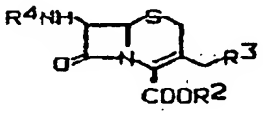
The present invention relates to elimination of a formyl group as the protective group of a nitrogen atom in cephalosporin derivatives.

The compound (2) obtained by the present invention is an excellent antimicrobial agent (JP-A-57/62287 and JP-A-60/67483) and can be obtained by elimination of a formyl group from the compound (1) (JP-A-60/67483). This elimination is carried out by treatment of the compound (1) with a mineral acid, but the purity of the compound (2) is lowered by production of by-products and decomposition of the compound (1) and/or the compound (2).

The present inventors have found that treatment of the compound (1) with methanesulfonic acid or trifluoromethanesulfonic acid affords the compound (2) in a high purity and completed the present invention based on such finding.

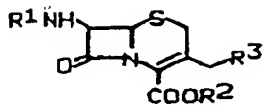
Construction of Invention:

The present invention provides a process for preparing a compound of the formula:



(2)

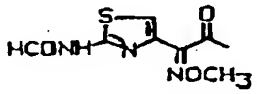
or its salt, which is characterized by treating a compound of the formula:



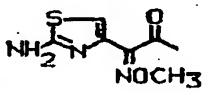
(1)

with methanesulfonic acid or trifluoromethanesulfonic acid.

In the above formulas, R1 is a formyl group or a group of the formula:



, R2 is a 1-alkoxycarbonyloxyethyl group or an anion, R3 is an alkoxy group or a thazolio group optionally substituted with alkyl and/or hydroxyalkyl and R4 is a hydrogen atom or a group of the formula:



The alkyl moiety in the 1-alkoxycarbonyloxyethyl group represented by R2, the alkoxy group and the hydroxyalkyl group as the substituent on the thiazolio group represented by R3 and the alkyl group as the substituent on the thiazolio group represented by R3 may be, for instance, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl or t-butyl.

As the salt of the compound (2), there are exemplified hydrochloride, sulfate, methanesulfonate, trifluoromethanesulfonate, etc.

The compound (2) can be obtained by the procedure as set forth below.

The compound (1) is dissolved or suspended in a solvent, and 1 to 5 equivalents, preferably 2 to 3 equivalents, of methanesulfonic acid or trifluoromethanesulfonic acid are added thereto. The resulting mixture is

kept at a temperature of 0 to 50℃, preferably of 20 to 40℃, for a period of 10 minutes to 2 hours. The reaction mixture is treated in a customary manner to give the compound (2).

The solvent to be used in the reaction of this invention may be, for instance, methanol, ethanol, propanol, isopropanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane or toluene.

Effect of Invention:

Compared with the known process, the process of the invention accomplishes the reaction with a milder condition so that the by-products and the decomposition products are given in smaller amounts and the compound (2) can be obtained in a higher purity. Since the amount of the by-products and the decomposition products is smaller, the yield of the compound (2) is better.

Practical embodiments of the present invention will hereinafter be illustrated by way of examples.

Example 1

(RS)-1-(Isopropyloxycarbonyloxy)ethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetadmido]-3-methoxymethyl-3-cephem-4-carboxylate

The starting formyl compound in a dry state (32.6 g) is suspended in methanol (197 ml), and methanesulfonic acid (10.6 g; 2 eq.) is added thereto while keeping the inner temperature at 25± 1 ℃, followed by stirring while keeping at the same temperature. After 30 minutes, the reaction mixture is made uniform, and the reaction is completed. To the reaction mixture, water (650 ml) and activated carbon (6.5 g) are added and stirred well, followed by filtration. The filtrate is adjusted with ammonia water or aqueous carbonic acid solution to pH 5.5 ~ 6.0. After cooling to 10℃, stirring is continued for 1 hour, and filtration is effected. The collected produced is washed with water and dried under reduced pressure to give the objective compound (28.0 g). Yield, 90 %; content, 96 %.

During the above operation, there are by-produced the Δ^2 compound and the E form (anti-form) on the 7-substitution in an amount of 0.1 to 0.2 %. When the reaction is effected using a mineral acid, e.g. hydrochloric acid, it takes 4 hours until the reaction is completed, and the amount of the Δ^2 compound and the E form (anti-form) as by-produced reaches to 1 %. In addition, other decomposition products are also by-produced. Thus, depression of the purity of the compound (2) is observed in comparison with the process of the invention.

NMR spectrum ($CDCl_3$, δ p p m) :

1.33(6H,d,J=5Hz), 1.59(3H,d,J=5Hz),
3.34(3H,s), 3.58(2H,s), 4.04(3H,s),
4.35(2H,s), 4.92(1H,m), 5.08(1H,d,J=3.5Hz),
5.27(2H,d,J=3.5Hz), 6.01(1H,m), 6.88(1H,s),
6.95(1H,q,J=6Hz), 7.31(1H,d,J=4Hz)

Example 2

7-Amino-3-[3-(4-methyl-5-(2-hydroxyethyl)thiazolio]methyl-3-cephem-4-carboxylate
hydrochloride

The starting formyl compound hydrochloride (32.8 g) is dissolved in methanol (330 ml), and methanesulfonic acid (15 g) is added dropwise thereto. The reaction is effected at 40℃ for 40 minutes. After cooling to 0 ~ 5℃, triethylamine (15.8 g) is added thereto at the same temperature, followed by stirring for further 1.5 hours. The precipitated crystals are collected by filtration, washed with cold methanol (66 ml) and dried under reduced pressure to give the objective compound (20.2 g).

NMR spectrum (d^6-DMSO, δ p p m) :

2.47(3H,s), 2.8~4.0(6H,m),
5.10(1H,d,J=4.5Hz), 5.35(2H,br),
5.62(1H,d,J=4.5Hz), 10.20(1H,s)

Example 3

7-Amino-3-(3-thiazolio)methyl-3-cephem-4-carboxylate hydrochloride
7-Formamido-3-(3-thiazolio)methyl-3-cephem-4-carboxylate hydrochloride (3.6 g) is dissolved in ethanol (50 ml), and methanesulfonic acid (1.5 g) is added dropwise thereto. The reaction is effected at 40℃ for 30 minutes. After cooling to 0 ~ 5℃, triethylamine (1.58 g) is added thereto, followed by stirring for further 1 hours. The precipitated crystals are collected by filtration, washed with cold ethanol (10 ml) and dried under reduced pressure to give the objective compound (2.87 g).

NMR spectrum (d^6-DMSO, δ p p m) :

2.8~3.5(2H), 5.02(1H,d,J=4.5Hz),
5.1~5.5(2H), 5.70(1H,m), 7.10(2H,br),
8.1~8.4(1H,m), 8.7~9.1(1H,m),
10.3~10.6(1H,m)

Example 4

7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3- [5-(2-hydroxyethyl)-4-methylthiazoliomethyl]-3-cephem-4-carboxylate
The starting formyl compound (40 g) is dissolved in methanol (400 ml), and methanesulfonic acid (19 g) is added thereto, followed by stirring at room temperature for 30 minutes. After cooling to 0 ~ 5℃, triethylamine (28 ml) is added thereto, followed by stirring for further 1 hour. The precipitate is collected by filtration, washed with cold methanol (10 ml) and dried under reduced pressure to give the objective compound (33 g).

NMR spectrum (d^6-DMSO, δ p p m) :
2.39(3H,s), 3.20(2H,t,J=5Hz), 3.38(2H,s),
3.65(3H,t,J=5Hz), 3.83(3H,s),
5.18(1H,d,J=5Hz), 5.39~5.54(2H,m),
5.85(1H,dd,J=5Hz,8Hz), 6.73(1H,s), 7.22(2H,s)